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## 3D and Subtraction MR imaging in Multiple Sclerosis

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**Summarizing discussion,  
Implications and Technical  
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improvements**

# Chapter 6

## 6.1 | Summarizing discussion

The goal of the research presented in this thesis was to improve the detection of spatiotemporal disease activity in the MS brain, by using more sophisticated acquisition and post-processing techniques. This could have important implications for both the radiological practice and for clinical trial design. In Chapter 2, we first evaluated the use of conventional 2D techniques in large multi-center trials, both for the detection of (MS) brain lesions, and for determining the predictive value of MRI variables for the diagnosis of MS. Secondly, in Chapter 3, we used single-slab 3D MR imaging to improve the spatial detection of both gray matter (GM) and white matter (WM) MS lesions throughout the whole brain, and also specifically within the hippocampus. Thirdly, in Chapter 4, we used subtraction MR imaging, to improve the temporal detection of active MS lesions, and compared this technique with conventional 2D images for the evaluation of treatment efficacy. Finally, in Chapter 5, we combined single-slab 3D and subtraction MR imaging in order to provide an optimal imaging strategy for the detection of spatiotemporal disease activity in MS

### Chapter 2 | Detection of (MS) brain lesions using conventional 2D MR imaging

In this chapter we used conventional MR images from large multi-center studies, namely the natalizumab safety evaluation <sup>1</sup>, which included 1169 patients with Crohn's disease (CD) and rheumatoid arthritis (RA), and the BENEFIT study <sup>2</sup>, which included 468 patients with a first clinically isolated syndrome (CIS) suggestive of MS. RA, CD and MS are all autoimmune disorders, thought to develop against a shared background of generalized susceptibility to autoimmunity <sup>3</sup>. All three diseases can cause WM lesions within the brain, either through inflammation and demyelination or through vasculitis. In this chapter we quantified the number of abnormalities in the brain using conventional 2D sequences, and evaluated associations with possible causative disease markers and clinical outcome.

#### Chapter 2.1

The study presented in this chapter represents a quantification of the number of incidental findings, including white matter changes (WMC) on conventional brain MR images of patients with CD and RA. Furthermore, associations between WMC scores and etiological parameters (demographic, vascular, disease-related, and treatment) were explored. Compared with prevalence rates reported in the literature in healthy populations <sup>4,5</sup>, the

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occurrence of incidental tumors was not apparently increased in our CD or RA cases, while the prevalence of cerebral infarcts seemed slightly increased in RA. We found WMC to be present in 43.9% of CD patients and 62.6% of RA patients. Of the etiological parameters examined age was most strongly associated with WMC scores in both CD and RA. There are reports of various types of treatment causing WMC in both CD and RA <sup>6-8</sup>. However, in this study we did not find any significant association between WMC and any specific sort of treatment. Also, there are various reports that the prevalence of MS is higher in both CD and RA than to be expected by mere chance <sup>3,9-12</sup>. In our study, subclinical, multi-focal MS-like lesions were indeed more common than would be expected from population-based clinical MS prevalence rates. This finding reinforces the theorem of a similar genetic background in patients with autoimmune disorders, although no clear mutual genetic cause for MS, CD and RA has yet been identified.

## Chapter 2.2

In this study we focused solely on CIS patients, at high risk for developing MS. MRI is known to be a powerful prognostic tool, and is frequently used to estimate the probability that these patients convert to CDMS. The modified Barkhof criteria <sup>13,14</sup>, representing a prognostic model based on typical MRI findings, have been incorporated into the International Panel (IP) criteria for the diagnosis of MS <sup>15,16</sup>. However, the influence of early disease-modifying treatment on the prognostic value of the criteria is not clear, nor is the ideal timing for follow-up scans. We assessed the prognostic value of baseline and follow-up MRI variables in 468 CIS patients, who received either early or delayed treatment, for conversion to CDMS after 3 years. In general, the percentage of patients converting to CDMS was higher in the presence, compared with the absence, for all baseline MRI variables investigated. In particular, the presence of at least nine T2 lesions in the brain was a strong predictor, next to the spatial distribution of T2 lesions, for example the presence of more than three periventricular lesions. However, there was no specific advantage for a fixed cut-off point of three or more fulfilled Barkhof criteria, currently imposed in the IP criteria to ascertain dissemination in space (DIS). This could be reflective of using the integrated three year data, in which all patients received at least one year of open-label treatment, lowering overall conversion rates. An overall lower event rate will lead to a lower predictive value for any prognostic variable studied. Also, compared with previous studies, we used statistical models with covariate adjustment, which lowered the predictive value of the MRI variables studied. Secondly, we found that the prognostic value of MRI criteria was

unaffected treatment intervention. Thirdly, follow-up MRI, to ascertain dissemination in time (DIT), was most informative after 9 months, and in patients *without* DIS at baseline. This might be reflective of the interrelation between DIS, DIT and CDMS, i.e. patients *with* DIS at baseline already have a higher chance compared with patients *without* DIS to convert and hence the additional risk of new lesions at follow-up MRI might be lower.

### **Chapter 3 | Improved detection of spatial disease activity using single-slab 3D imaging**

The previous studies confirm the (predictive) value of conventional 2D MR sequences. Although conventional 2D sequences still are the cornerstone of MS imaging protocols, the last decade has seen an increasing number of studies describing more modern acquisition techniques able to improve the detection of MS lesions in various parts of the brain. For example, the spatial detection of WM lesions can be improved by using 3D sequences, especially when combined with image contrasts such as fluid-attenuated inversion-recovery (FLAIR) <sup>17,18</sup>. In addition, a *multi-slab* 3D double inversion-recovery (DIR) sequence demonstrated an increased detection of GM lesions, although this sequence initially suffered from long acquisition times, and flow and slice profile artifacts. A *single-slab* 3D technique was later developed <sup>19</sup>, with shorter acquisition times and absence of flow artifacts <sup>20</sup>, which has been adapted to include various contrasts <sup>21</sup>. These more modern 3D sequences show great promise, but if they are to replace conventional 2D MR sequences in MS imaging protocols, they should be extensively evaluated for the detection of spatial disease activity and the detection of temporal disease activity. In Chapter 3, we focused on the first point, and the detection of MS lesions was cross-sectionally examined using single-slab 3D MR imaging, both in the whole brain and specifically in the hippocampus. 3D results were compared with conventional 2D MR imaging.

#### **Chapter 3.1**

In this chapter we described the signal and contrast properties of an isotropic, single-slab 3D dataset (DIR, FLAIR, T2, and T1w magnetization prepared rapid acquisition gradient-echo MPRAGE), and evaluated its performance in detecting MS brain lesions, compared with conventional 2D-T2SE. In general, improved signal and contrast properties of the 3D sequences enabled an increased detection of MS lesions in various parts of the brain. Specifically, 3D-DIR showed the highest detection of intracortical and mixed WM-GM

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lesions, whereas 3D-FLAIR showed the highest total number of WM lesions. Furthermore, (intra)cortical lesions were also visualized with 3D-MPRAGE. Probably a conducive factor was the decrease in slice thickness, 3 mm for the 2D sequences compared with 1.3 mm for the 3D sequences, which is strongly associated with increased lesion detection <sup>22,23</sup>. Furthermore, the highest numbers of infratentorial lesions were scored on 3D-DIR and 3D-FLAIR images. This was related to the absence of blood and CSF flow artifacts in the 3D sequences, especially in the posterior cranial fossa, which is explained by the single-slab nature of the sequence employing non-spatially selective radio-frequency pulses <sup>20</sup>. Based on this study we proposed that a selection of single-slab 3D contrasts, for example 3D-FLAIR and 3D-DIR, could replace 2D sequences in the radiological practice.

### Chapter 3.2

The hippocampus is a deep GM structure thought to play a central role in memory functions <sup>24</sup>. Memory functions can be impaired in MS patients <sup>25-27</sup>, which could be reflective of hippocampal demyelination, which was indeed found in a recent histopathology study <sup>28</sup>. In the study presented in Chapter 3.2, we exploited the intrinsic advantage of our 3D sequences with nearly isotropic voxel dimensions, by orthogonally reformatting the 3D images without loss of image quality, to select an optimal viewing plane for the hippocampus. We used 3D-DIR images because our previous study (Chapter 3.1) showed that DIR yields the highest detection of GM lesions. We found that 14 (88%) of the 16 MS patients examined had at least one hippocampal lesion, with an average of 2-3 hippocampal lesions per patient. Furthermore, only 56% of the hippocampal lesions identified on the 3D-DIR images, could also be identified on the 3D-T2 images. As such, orthogonally reformatted 3D-DIR images allowed the visualization of hippocampal lesions in vivo. This now allows future studies to better examine the role of hippocampal damage in cognitive decline, most notably memory impairment, in MS.

### Chapter 4 | Improved detection of temporal disease activity using 2D Subtraction MR imaging

In this chapter we focused on improving the detection of temporal disease activity using subtraction MR imaging. The concept of subtraction imaging is that the baseline image is *subtracted* from a follow-up image to create an “image of change”. Subtraction imaging has some inherent advantages, such as the reduction of repositioning errors,

and cancellation of the non-active background (Chapter 1.3.2). However, one needs an accurate registration procedure, as the subtraction image would otherwise mostly consist of misregistration artifacts, as well as intensity homogeneity procedures to correct for coil inhomogeneity and scanner drift.

So far, subtraction imaging has successfully been applied using *single-center*, 2D MR images<sup>29,30</sup>. The two studies presented in this chapter used MR images from *multi-center* trials acquired with different MR systems, presenting additional challenges for image postprocessing methods due to scanner-dependent variations in image contrast. These were successfully overcome by our pipeline, which is described in the introduction of this thesis (Box 3). In this chapter we longitudinally examined the detection of active MS lesions and evaluated treatment efficacy using 2D subtraction MR imaging, compared with non-registered, conventional 2D-T2SE images (Chapter 4.1) and serial monthly gadolinium-enhanced T1w (Gd-T1w) imaging (Chapter 4.2).

#### Chapter 4.1

When subtraction images were used, there was a 1.7-fold increase in the detection of positive active (new and enlarged) lesions, as compared with unregistered images. Furthermore, such lesions were detected with a significantly greater interobserver agreement. Subtraction imaging allowed the direct quantification of positive and negative disease activity demonstrating that overall disease activity can be severely underestimated on native images. Moreover, the direct volumetric analysis of positive active lesions on subtraction images provided a more sensitive method to detect treatment effects, compared with a standard measurement of total lesion load change on unregistered images. The increased power to detect treatment effects found in this study could translate into a possible reduction in the number of patients and/or follow-up examinations needed for clinical trials.

#### Chapter 4.2

In this study we examined MRI data over 9 months from 116 patients. Long-interval (over nine months) T2-weighted subtraction (T2w-Sub) images were compared with monthly Gd-T1w imaging for the detection of active lesions and treatment effects. The numbers of T2w-Sub lesions and the cumulative number of new Gd-T1w lesions detected were significantly correlated, albeit that subtraction imaging detected around half of the lesions compared with Gd-T1w imaging. Despite this loss in sensitivity, we found long-

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interval T2w subtraction MR imaging to exhibit increased power to detect treatment effects, compared with serial monthly Gd-T1w imaging. T2w subtraction MR imaging could greatly increase the cost-effectiveness of clinical trials, by limiting the number of patients, contrast injections and MRI scans needed, and decrease patients' risk by obviating repetitive gadolinium administration.

## **Chapter 5 | Improved detection of spatiotemporal disease activity using 3D Subtraction MR imaging**

Notwithstanding the benefits of 2D subtraction images, as mentioned in previous chapters, the quality of subtraction images and hence the detection of active lesions, could be further ameliorated by the application of isotropic 3D images, because the major drawback of 2D-T2SE images is the anisotropic voxel size which reduces the accuracy of the registration procedure. Furthermore, 2D-T2SE images suffer from blood and CSF flow artifacts in the posterior cranial fossa which are inconsistent over time, leading to artifacts in the subtraction image. 3D sequences allow the acquisition of smaller, isotropic voxels while maintaining a good signal-to-noise ratio (SNR). In particular, single-slab 3D sequences that apply non-spatially selective radio-frequency pulses with variable flip angles, thereby minimizing flow artifacts, are of specific interest for the creation of subtraction images.

As such, we combined single-slab 3D imaging, which provided an increased detection of spatial disease activity (Chapter 3), with subtraction MR imaging, which provided an increased detection of temporal disease activity (Chapter 4), in order to provide an optimal imaging strategy for the detection of spatiotemporal disease activity in MS. In this final chapter we compared 3D subtraction imaging with 2D subtraction imaging, to examine whether the aforementioned benefits of using isotropic 3D sequences for the creation of subtraction imaging culminates in a higher detection of active MS lesions.

### **Chapter 5.1**

We acquired 3D (DIR, FLAIR, T2, T1-MPRAGE) and 2D sequences in fourteen patients and nine age-matched healthy controls. We found that 3D subtraction images suffered less from residual misregistration and flow artifacts, resulting in better image quality, compared with 2D subtraction imaging. This resulted in an increased detection of active MS lesions using 3D subtraction imaging. Among the 3D sequences, 3D-MPRAGE subtraction



imaging detected significantly higher numbers of (positive) active MS lesions, especially small and infratentorial lesions. Our results showed that 3D subtraction imaging could be a promising technique to increase sensitivity in ascertaining dissemination in time, and to increase the power of MRI-monitored treatment trials in MS.

## **6.2 | Clinical implications**

In this thesis we have presented more modern and sophisticated MRI and postprocessing techniques that better visualize the spatiotemporal disease activity in MS. Based on the results of this thesis, a new MS imaging protocol could be tentatively envisaged, replacing conventional 2D sequences. Such an improved MS imaging protocol could consist of three single-slab 3D contrasts, namely 3D-DIR, 3D-FLAIR and 3D-MPRAGE. This would enable an optimal detection of GM and WM lesions in both space and time, especially when combined with subtraction imaging. Since the introduction of the IP criteria, the diagnosis of MS in CIS patients can be made largely on radiological grounds. This means that any imaging technique that improves the cross-sectional or longitudinal detection of MS lesions, will also have an effect on the number of patients fulfilling DIS or DIT criteria respectively. Using the aforementioned new imaging protocol, future studies should aim to confirm the expected increase in sensitivity in ascertaining DIS and DIT, and hence in diagnosing MS. Secondly, the predictive value for clinical measures, such as conversion to clinically definite MS and clinical disability, should be examined.

Currently, the modified Barkhof criteria require the presence of one or more juxtacortical lesions. Now that new MR sequences exist that are better able to detect (intra)cortical and mixed WM-GM lesions, the predictive value of these lesions for conversion to CDMS should be examined. However, to systematically study GM lesions, consensus guidelines should be formulated, that clearly describe how to identify cortical GM lesions on DIR, and MPRAGE images. Furthermore, it would be interesting to evaluate the risk increase for CDMS provided by DIT when evaluated with the MS imaging protocol proposed above, especially when combined with subtraction imaging. Does the expected increased sensitivity to determine DIT also lead to more predictive power for conversion to CDMS? Possibly, DIT could also be determined within a shorter time-interval, allowing for a more rapid treatment intervention.

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On a more fundamental note, the IP criteria to determine DIS are based on the Barkhof criteria, which were presented more than a decade ago <sup>13</sup>. Seventy-four CIS patients were examined with mostly 0.5T and 0.6T MR systems, with a slice thickness ranging from 5 to 10 mm. A cumulative chance model was presented, consisting of four dichotomized MRI criteria, to optimally predict conversion to CDMS. These criteria, although slightly modified by Tintoré et al <sup>14</sup>, are still in use, even though the last twelve years have seen a wide array of technological improvements. The majority of MR systems now operate at 1.5T minimally, and coil designs have become more advanced. Furthermore, more modern sequences and contrasts are now available. All these factors should result in an increased sensitivity for MS brain lesions. Interestingly, the (modified) Barkhof criteria have been extensively evaluated since 1997, and efforts have been made to simplify MRI criteria <sup>31,32</sup>, but the underlying statistical analysis, which presented the final four criteria (of 15, including lesion characteristics such as location and size), has been repeated only once. In a recent paper, Korteweg et al. found that a statistical model including two periventricular and three deep white matter lesions yielded the highest diagnostic accuracy <sup>33</sup>. However, this study still used conventional MR sequences acquired with relatively thick image slices of 3 to 5 mm, and cortical GM lesions were not accounted for. Hence, it would be interesting to undertake a similar statistical analysis as done in 1997, with the aforementioned 3D MS imaging protocol. It would be interesting to investigate whether the same four dichotomized MRI criteria still provide the most optimal model to predict conversion to CDMS in CIS patients, when using the proposed, newer 3D dataset.

So far, correlations reported between clinical disability and conventional MRI variables are only weak to moderate <sup>34</sup>. It has been postulated that an increased detection of small lesions, especially those in eloquent brain areas, might improve these correlations. Alternatively, one could speculate that larger lesions, already detected with conventional 2D imaging, cause more extensive damage and likely contribute more to disability measures. In this regard, GM lesions could be of special interest as well, as post-mortem MRI studies have shown that GM lesions are mostly missed with conventional 2D sequences <sup>35</sup>. 3D-DIR imaging can be used to improve the detection of GM lesions, as demonstrated in Chapter 3 of this thesis. Indeed, recent studies have reported that (intra) cortical lesions are associated with higher clinical disability and cognitive impairment <sup>36,37</sup>. Of the conventional MRI measures T1-hypointense lesions, so-called ‘black holes’, have so far shown strongest correlations with clinical disability <sup>34,38</sup>. The 3D imaging

protocol presented in this thesis includes T1-weighted 3D-MPRAGE images, which should be further evaluated to determine the behavior and predictive value of T1-hypointense lesions detected with this sequence, especially in comparison with conventional 2D-T1w sequences. 3D T1-based sequences (such as MPRAGE) should also be further investigated for their potential to detect and possibly subclassify GM lesions, which may substantially improve correlations with clinical disability.

Finally, this thesis compared 3D and subtraction MR imaging with conventional (non-subtracted) 2D MR imaging. As such, this thesis did not study all MRI techniques currently used to assess MS disease activity. For example, spinal cord imaging is routinely used in the clinical practice. Spinal cord abnormalities are abundant in MS patients, and are rare in other neurological diseases. Using spinal cord imaging therefore increases the sensitivity and specificity of diagnostic MRI criteria for MS <sup>39,40</sup>, which has e.g. resulted in a more liberal role for spinal cord lesions in the 2005 revisions to the IP criteria; spinal cord lesions may now contribute, together with brain lesions, to reach the required number of nine T2 lesions, and can be replacement for an infratentorial lesion <sup>16</sup>. As such, the proposed new MS 3D imaging protocol should predominantly be seen as a replacement of the conventionally used 2D sequences, and when introduced into the clinical setting, should be complemented with spinal cord and post-contrast imaging.

### 6.3 | Implications for clinical trial design

In clinical trials, the reduction of the number of active MRI lesions is used to evaluate anti-inflammatory properties of new MS drugs. Phase II trials use serial gadolinium-enhanced T1w imaging, and phase III trials supplementary use T2w imaging. The cost-effectiveness of clinical trials could be increased by MRI measures that are able to more sensitively detect treatment effects. The increased power could namely be used to reduce the number of patients and scans needed. In **Chapter 4** we found T2w subtraction imaging to demonstrate an increased power compared with 1) non-registered T2w scans, and 2) serial gadolinium-enhanced T1w imaging, to determine treatment efficacy. As such, T2w subtraction imaging could greatly increase the cost-effectiveness of both phase II and phase III trials, and by obviating gadolinium injections (*Chapter 4.2*) T2w subtraction imaging could also increase patient safety.

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Compared with serial gadolinium-enhanced T1w imaging long-interval T2w subtraction imaging could have potential limitations. Firstly, the loss of temporal information regarding drug effectiveness during the trial, i.e. when are treatment effects first seen on monthly MRI variables. Secondly, with a very potent agent demonstrating significant treatment effects before the official end of the trial, you miss the option for early termination. However, the results presented in this thesis give impetus for the use of (long-interval) T2w subtraction imaging as an outcome measure in clinical MS trials and future studies should elaborate on the advantages and possibly disadvantages.

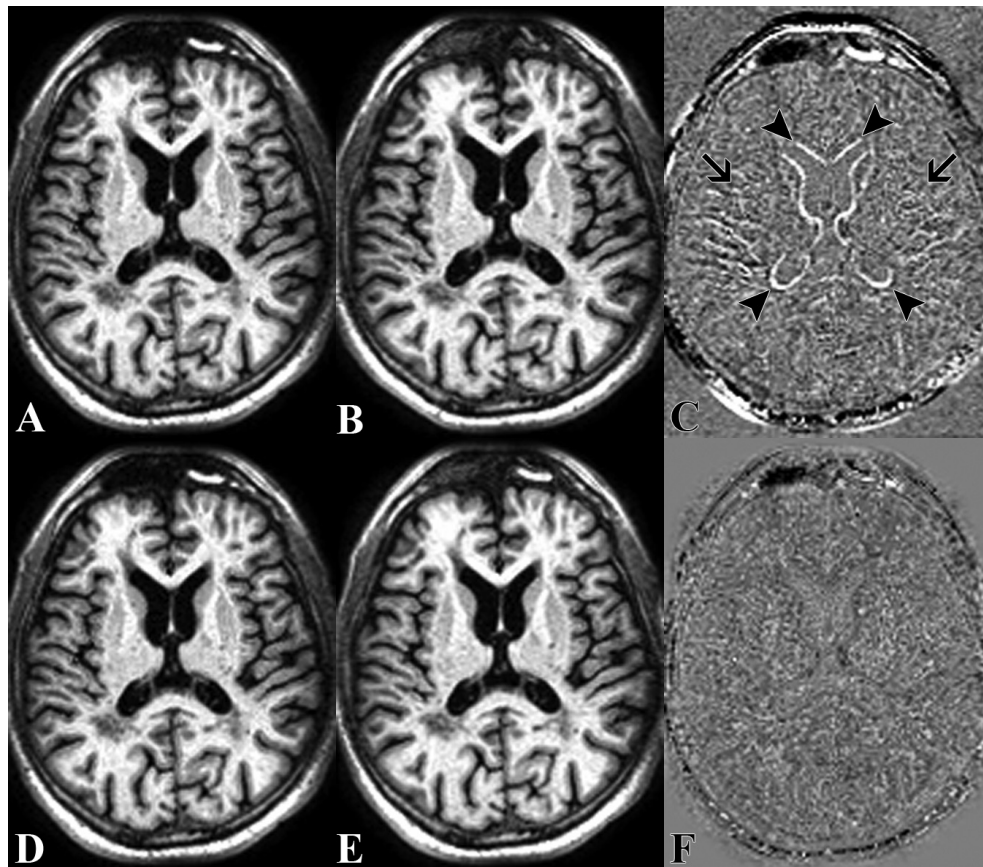
## 6.4 | Technical limitations and future improvements

The pipeline used for the creation of subtraction images as presented in this thesis has some potential limitations. First, it uses a linear registration method. This allowed an accurate registration in the studies presented in this thesis, as the time between consecutive scans was relatively short, ranging from 3-9 months. In this time-interval hardly any brain atrophy will have occurred. However, brain atrophy is likely to be more pronounced with longer scan intervals, and linear registration methods perform suboptimally in case of substantial brain atrophy, especially if the atrophy is distributed across the brain in a nonuniform fashion. Hence, future studies should also investigate the use of non-linear registration methods, such as fluid registration <sup>41</sup>, which are able to better match regional deformities (Figure 1). Furthermore, such a method can also be used to display disease activity in alternative ways, i.e. by showing stretch maps, indicating contraction or expansion per voxel, derived from the deformation field needed to register the follow-up image to the baseline image (Figure 2). The stretch maps are subsequently inverted and projected over the baseline image since the method is mostly used in Alzheimer's disease to identify areas susceptible to atrophy effects. Secondly, the studies presented in this thesis were conducted in a research setting, in which the time needed to conduct image post-processing was not of crucial interest. However, to introduce these techniques into a clinical setting, faster methods are needed. Ideally, postprocessing can be directly performed on the viewing console of the MR scanner, allowing the radiologist near immediate access to subtraction images. Two steps could facilitate this process. Firstly, the use of a uniform file format in image postprocessing. Changing the file format between consecutive post-processing steps increases computational time.

This has been initiated with the introduction of the nifti (.nii) file format, but should be further explored. Secondly, computational time can be reduced by using more powerful hardware, ideally in a parallel setup, so that the computational power of more than one computer can simultaneously be accessed.

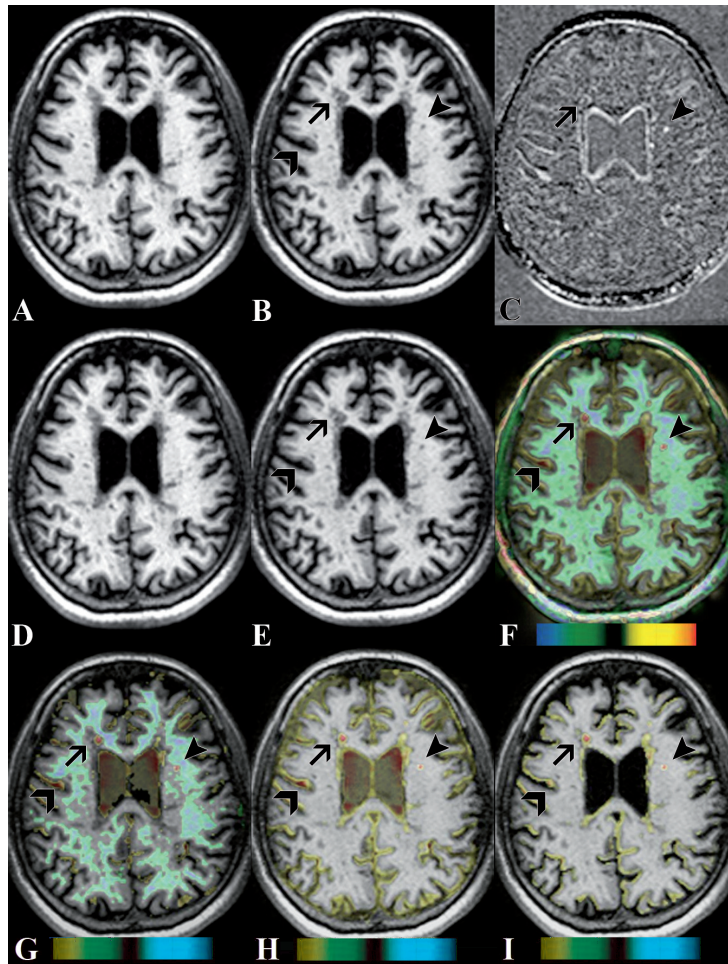
The detection of MS lesions in the brain could be further improved by methods able to acquire MR images with further increased SNR, allowing higher image resolution, i.e. a smaller voxel size. The studies described in this thesis were performed at 1.5T, the dominant clinical field strength, using a standard circularly polarized head coil. Increased SNR might be obtained either by increasing the field strength or by using multi-channel phased array coils. Cross-sectional studies comparing 1.5T with 3T and 7T found an increased detection of MS lesions in the brain of 13% and 23% respectively <sup>42,43</sup>. Furthermore, the extent of cortical pathology <sup>43</sup> and the relationship with microvasculature <sup>44</sup> was better visualized at 7T. Nevertheless, the acquisition of MR images at high field is complicated by specific absorption rate (SAR) limitations, and increased susceptibility to inhomogeneity effects. The application of single-slab 3D sequences at high(er) field strength is interesting, because single-slab sequences use refocusing pulses with flip angles much less than 180°, reducing the SAR, compared with conventional (turbo) spin-echo sequences that use refocusing flip angles of 180° <sup>45</sup>. So far, high field strength images have not been used for the creation of subtraction images, nor has their increased potential for MS lesion detection been compared with that of subtraction imaging at 1.5T.

In conclusion, we have demonstrated that both single-slab 3D and subtraction imaging contribute to an improved detection of spatiotemporal disease activity in MS. Future studies will have to investigate whether the single-slab 3D dataset presented in this thesis can be standardly used in radiological practice, and whether 2D or 3D subtraction imaging can fully replace serial MRI comparisons of conventional 2D images in clinical trials. Although some technical issues have to be resolved regarding the implementation of these new methods, this thesis has laid a strong foundation stimulating further explorations.



**Figure 1** | Example of atrophy effects using linear registration over a 3 year time period. AD: halfway-registered baseline 3D-MPRAGE image; B: rigid-body halfway registered follow-up 3D-MPRAGE image; C: rigid-body subtraction image; E: FLUID registered follow-up image; F FLUID subtraction image. Whereas in the rigid-body subtraction image both central (arrowheads) and peripheral (arrows) atrophy effects are seen, these are corrected for in the FLUID registered subtraction image.





**Figure 2** | Example of alternative ways to detect MS disease activity over 3 years using non-linear FLUID registration. AD: halfway-registered baseline 3D-MPRAGE image; B: rigid-body halfway registered follow-up 3D-MPRAGE image; C: rigid-body subtraction image; E: FLUID registered follow-up image; FGH: halfway-registered baseline 3D-MPRAGE images overlaid with various FLUID stretchmaps. Color bars indicate up to 20% contraction (green to blue) or up to 20% expansion (yellow to orange) per voxel. F: normal stretchmap; G: showing only activity greater than 10%; H: showing only expansion; I: showing only expansion within brain parenchyma mask. Arrowheads: New lesion; Arrows: Possible disease activity within a pre-existing lesion; Delta arrows: CSF expansion hampering the detecting of active lesions, which are almost nullified by displaying only expanding voxels within the brain parenchyma mask.

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—— Summarizing discussion, Implications, and Technical limitations and future improvements

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